NOTE *Pathology*

Systemic Candidiasis and Mesenteric Mast Cell Tumor with Multiple Metastases in a Dog

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ABSTRACT. A 5-year-old female miniature dachshund presenting with persistent vomiting and diarrhea had two concurrent rare pathological conditions: systemic candidiasis and mesenteric mast cell tumor with multiorgan metastases. Neoplastic mast cells formed mass in the mesentery of the cecal-colonic region and were also found in the liver, spleen, kidneys, lungs, adrenal grands, ovaries, bone marrow and other tissues. The cells had intracytoplasmic granules with metachromasia and were immunohistochemically positive for c-kit and histamine. Granulomatous lesions with fungal organisms were present in the heart, lungs, kidneys, pancreas, subserosal and surrounding adipose tissue of the duodenum, thyroid glands and mesenteric mass, and phagocytosed organisms were detected in the liver and bone marrow. Bacteriologically and immunohistochemically, the fungi were consistent with *Candida albicans*.

KEY WORDS: candidiasis, canine, mast cell tumor.

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Candida is a normal inhabitant of the alimentary, upper respiratory, and genital mucosa of mammals and causes oppotunistic mycosis of the mucous membranes [4, 6, 11]. Cutaneous infection is another manifestation. Systemic dissemination is less frequent and reports of systemic candidiasis are limited in dogs [1, 3, 8, 9, 13, 16]. For the establishment of candidal infections, a variety of statuses with suppression of the host-defence mechanisms are considered as predisposing conditions [4, 6, 11]. Mast cell tumor (MCT) is one of the most common neoplasms in canine skin and those originating in extracutaneous organs such as the spleen, liver, and intestine were infrequently reported [5, 7]. In this paper, we describe a canine case with two rare conditions, systemic candidiasis and mesenteric MCT with multiorgan metastases, and discuss the possible association between candidal dissemination and generalized MCT.

A 5-year-old female miniature dachshund was brought to a veterinarian with persistent vomiting of two weeks' duration, and was administered an H2 receptor antagonist, antibiotics and corticosteroid for a month. Exploratory ventrotomy and gastrotomy revealed no causative lesions. The dog did not show an improvement in vomiting, and presented with diarrhea and progressive weight loss during the next three weeks while she was treated with an H2 receptor antagonist, antiemetic, antibiotics, corticosteroid, and parenteral alimentation via the jugular vein. A subcutaneous mass, about 1 cm in diameter, was detected at the right 5th mammary gland. Radiographs revealed an intraabdominal mass, about 5 cm in diameter, around the ileocecal junction and no abnormalities in the lung field. The ileocecal and cutaneous masses were sampled by fine needle biopsy and surgical excision, respectively. The tissues from the ileocecal mass revealed scattered cells infiltrating in collagenous tissue, but detailed morphology of the cells were not obtained due to severe artifact. The cutaneous mass was composed of proliferation of round to polygonal neoplastic cells mainly locating in the subcutaneous tissue and infiltrating into the dermis. The cells had amphophilic to faint pink, fine-granular cytoplasm without distinct cell boundaries, and round vesicular or condensed nucleus. Multinucleated tumor cells were rarely seen. The neoplastic cells in both tissues showed metachromasia by toluidine blue reagent and were diagnosed as MCTs. Venous blood samples were submitted for bacteriological culture and histamine mesurement to commercial laboratories. She was then additionally administered an H1 receptor antagonist, and imatinib mesilate intraperitoneally, but continued to present with vomiting and diarrhea with an increased amount of pleural fluid, and died two weeks later. The blood culture detected *Candida albicans*, and plasma histamine concentration was 919 *n*g/m*l*.

Grossly, there was a slightly increased amount of abdominal fluid and a white firm neoplasm, 5.5 × 5.5 × 2.5 cm in size, in the mesentery of the cecal-colonic region (Fig. 1). On cut surfaces, the mass showed partial hemorrhage and engulfed the mesenteric lymph nodes, and was discontinuous to the intestinal walls. The aortic lumber and medial iliac lymph nodes were enlarged to 2.0 and 0.7 cm in diameter, respectively. Serosal ecchymoses were scattered throughout the intestine. The renal cortex showed a rough appearance with hemorrhagic foci. In the medulla, small cysts including necrotic tissue, up to 2 mm in diameter, were arranged along the renal pelvis. The thoracic cavity con-

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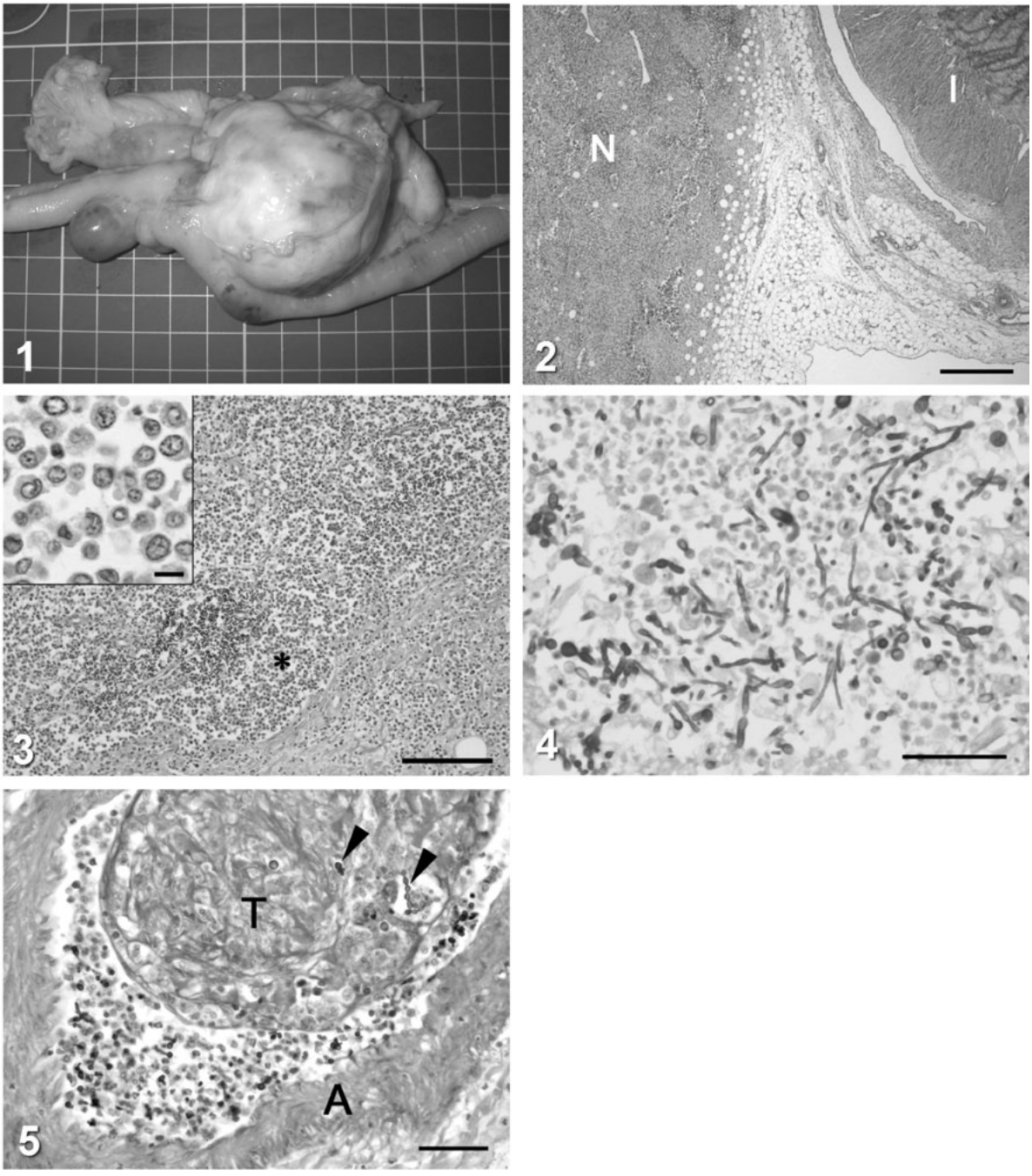

Fig. 1. An intraabdominal mass, 5.5 × 5.5 × 2.5 cm in size, located in the mesentery of the cecal-colonic region.

Fig. 2. Mesenteric mass. Neoplastic proliferation of mast cells (N) located in the mesentery and discontinuous to the ileum (I). Hematoxylin and Eosin (HE). Bar=500 μm.

Fig. 3. Mesenteric mass. Neoplastic mast cells fill the lymphatic sinus of the mesenteric lymph node (asterisk) and infiltrate in the surrounding fibroadipose tissue (lower right). HE. Bar=200 μm. (Inset) Higher magnification of the neoplastic cells in the sinus. The cells have round, ovoid, or cleaved nucleus and fine-granular cytoplasm. HE. Bar=10 μm.

Fig. 4. Heart. Oval to round blastospores, pseudohyphae comprising chains of elongated yeast-like structures, and tubular hyphae in the granulomatous lesion demonstrated with periodic acid-Schiff (PAS) reaction. Bar= 50 μm.

Fig. 5. Lung. Hyalin thrombus formation (T) associated with fungi (arrowheads) in the pulmonary artery (A). PAS reaction. Bar=50 μm.

tained a moderate amount of serosanguinous fluid and the lungs were diffusely edematous. Small white foci were scattered in the lungs, myocardium, and endocardium at the base of the arterioventricular valves. The right ventricle was moderately dilated.

Histologically, the mesenteric mass was composed of the proliferation of neoplastic mast cells on a background of fibroadipose tissue (Fig. 2). The background tissue had edema, hemorrhage and degeneration of collagen fibers. The mass included the mesenteric lymph nodes with indistinct boundaries and the lymphatic sinuses of the nodes were filled with neoplastic mast cells (Fig. 3). The cells had a round to cleaved, or bean-shaped, vesiculated nucleus and eosinophilic to amphophilic, fine-granular cytoplasm (Fig. 3 inset). Mitotic figures were 0 to 2 per high-power (× 400) field. Intracytoplasmic granules showed metachromasia with toluidine blue dye and were stained with periodic acid-Schiff reaction. Immunohistochemically, many cells showed intracytoplasmic granular staining with c-kit antibody (Dako Cytomation, Glostrup, Denmark) by avidin-biotin-peroxidase complex procedure followed by visualization with diaminobenzidine. Neoplastic cells had histamine in the cytoplasm demonstrated with anti-histamine antiserum (Cappel, Aurora, OH, U.S.A.). A few eosinophils were scattered between the neoplastic cells. Infiltrating mast cells were observed in the circumjacent mesenteric tissues but not in the adjacent intestinal walls. Neoplastic mast cells were also detected in the liver, spleen, kidneys, lungs, adrenal grands, ovaries, hepatic, pancreatico-duodenal, aortic lumber, and medial iliac lymph nodes, cardiac coronary adipose tissue, soft tissue around the trachea and esophagus, muscular layer to adventitia/serosa of the esophagus to duodenum, and sternal bone marrow. The skin from where the mast cell tumor was previously excised had no neoplastic cells.

Multiple white foci detected in the heart and lungs were consistent with granulomatous lesions. The lesions were composed of central necrosis, accumulation of neutrophils, macrophages, epithelioid cells, multinucleated giant cells, some lymphocytes, hemorrhage, and intralesional yeasts, pseudohyphae and hyphae free or ingested by the phagocytes. The mycotic organisms were lightly stained with hematoxylin and eosin, strongly with periodic acid-Schiff reaction (Fig. 4), and were immunohistochemically positive with monoclonal antibody against *Candida albicans* (Chemicon, Temecula, CA, U.S.A.). The lungs had multiple fungal emboli and hyaline thrombi (Fig. 5), and showed diffuse alveolar edema. In the renal medulla, some renal tubules were extremely dilated, forming cystic structures filled with mycotic organisms, neutrophils, macrophages and necrotic cell debris. The cysts partially ruptured and caused granulomatous reactions. Granulomatous lesions were also presented in the renal cortex, pancreas, subserosal and surrounding adipose tissue of the duodenum, thyroid glands, and mesenteric mass. Fungal organisms were detected in phagocytes in the liver and bone marrow. Hemorrhagic foci with neutrophils and macrophages without obvious fungi were scattered in the submucosa to serosa of the intestines. The liver showed a moderate degree of steroid hepatopathy. Focal erosion was observed in the stomach.

In this case, systemic fungal infections and metastatic MCT were concurrently detected. The fungi were bacteriologically and immunohistochemically proved to be *Candida albicans* but the portal of entry for infection was not clear. The histochemical and immunohistochemical properties of neoplastic cells were compatible with MCT. From the sizes and distribution of the neoplasms, and discontinuity of the mesenteric mass to the intestinal walls, the mesenteric connective tissue or lymph node was likely to be the primary site of the tumor, although cutaneous MCT was evident. Reported cases of canine intraperitoneal MCT, except for the gastrointestinal type, include those originating in the cranial mesenteric lymph node [2] and hepatopancreatic lymph node [15], so this case is rare. From histological examinations, the direct cause of death was pulmonary edema associated with pulmonary fungal embolism, thrombosis and multiple intramyocardial granulomas.

In the pathogenesis of local and disseminated candidiasis, various conditions that compromise host-defence mechanisms are considered to be a prerequisite, including the upset of normal endogenous microflora, disruption of mucosal or cutaneous barriers, neutropenia, and prolonged immunosuppression [4, 6, 11]. In canine systemic candidiasis, pretreatment with antibiotics and corticosteroids [8, 9], usage of parenteral catheters [8], ongoing diabetes mellitus [8], and previous parvovirus infection [16] were suggested to induce infection. In addition to these phenomena, it is necessary to establish metastatic lesions that candidal organisms pass across the vascular cell lining from the blood stream to organ parenchyma [12, 18]. Mast cells release various chemical mediators causing a variety of biochemical effects [17]. Histamine and serotonin provoke an increase in vascular permeability through vasodilation and endothelial cell contraction, i.e. expansion of interendothelial junctions [14, 17]. In this dog, the plasma histamine level was extremely high (919 *n*g/m*l*) [10] and histamine was detected in neoplastic mast cells. The administration of antibiotics and corticosteroid, and intravenous alimentation via the parenteral catheter were indeed risk facters for candidiasis, and it is possible that the expansion of intraendothelial junctions by mediators from neoplastic mast cells might facilitate the systemic dissemination of candidal infection.

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